Proposed synopsis on

NOVEL APPROACH IN DESIGNING AND DEVELOPMENT OF CONTROLLED RELEASE ORAL FORMULATION CONTAINING NATURAL POLYMERS

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ABSTRACT

The traditional use of excipients in drug formulations was to act as inert vehicles to provided necessary weight, consistency and volume for the correct administration of the active ingredient, but in modern pharmaceutical dosage forms they often fulfill multi-functional roles such as modifying release, improvement of the stability and bioavailability of the active ingredient, enhancement of patient acceptability and ensure ease of manufacture. New and improved excipients continue to be developed to meet the needs of advanced drug delivery systems. Polymers have been successfully investigated and employed in the formulation of solid, liquid and semi-solid dosage forms and are specifically useful in the design of novel drug delivery systems. Present study is a sincere effort with an aim to design and develop some novel controlled release oral formulations by using certain natural polymers isolated from natural sources. It is also planned to evaluate the formulation by various physical and mechanical methods followed by evaluating their drug release studies.

Key words: - Controlled release, Oral formulation, Natural polymers, Evaluation.

1) INTRODUCTION

1.1 Introduction to Oral Controlled Release Drug Delivery Systems:-

Oral ingestion is traditionally preferred route of drug administration, providing a convenient method of effectively achieving both local and systemic effects. Most conventional oral drug products, such as tablets and capsules, are formulated to release the active drug immediately after oral administration, to obtain rapid and complete systemic drug absorption. Such immediate-release products result in relatively rapid drug absorption and onset of accompanying pharmacodynamic effects. However, in conventional oral drug delivery systems, there is very little control over release of drug. After complete absorption of the drug from the dosage form, plasma drug concentrations decline according to the drug's pharmacokinetic profile. Eventually, plasma drug concentrations fall below the minimum effective plasma concentration (MEC), resulting in loss of therapeutic activity. Before this point is reached, another dose is usually given if a sustained therapeutic effect is desired[1].

In order to overcome this drawback of conventional drug delivery systems, several technical advancements have led to the development of Controlled release Oral drug delivery system that could revolutionize method of medication and provide a number of therapeutic benefits.

Oral controlled release drug delivery is a system that provides continuous oral delivery of drugs at predictable and reproducible kinetics for a predetermined period throughout the course of GI transit and also the system that target the delivery of a drug to a specific region within the GI tract for either a local or systemic action.

An ideal oral drug delivery system should steadily deliver a measurable and reproducible amount of drug to the target site over a prolonged period. Controlled release (CR) delivery system provides a uniform concentration or amount of the drug at the absorption site and thus,

after absorption allow maintenance of plasma concentrations within a therapeutic range, which minimizes side effects and also reduces the frequency of administration[2].

Advantages of Controlled Drug Delivery Systems:

- Maintenance of plasma drug concentration within an optimal therapeutic range for prolonged duration of treatment.
- More consistent and prolonged therapeutic effect is observed.
- Maximization of efficiency-dose relationship.
- Employ less total drug than that in combined conventional dosage forms.
- Reduction of adverse side effects.
- Minimization of the need for frequent dose intake.
- Improved patient compliance.
- Improves control of condition i.e., reduced fluctuation in drug level.
- Minimize or eliminate local side effects
- Minimize drug accumulation with chronic dosing.
- Make use of special effects, e.g. Sustained-release aspirin for morning relief of arthritis by dosing before bed time.
- Economy i.e. reduction in health care costs. The average cost of treatment over an extended time period may be less, with lesser frequency of dosing, enhanced therapeutic benefits and reduced side effects.[3]

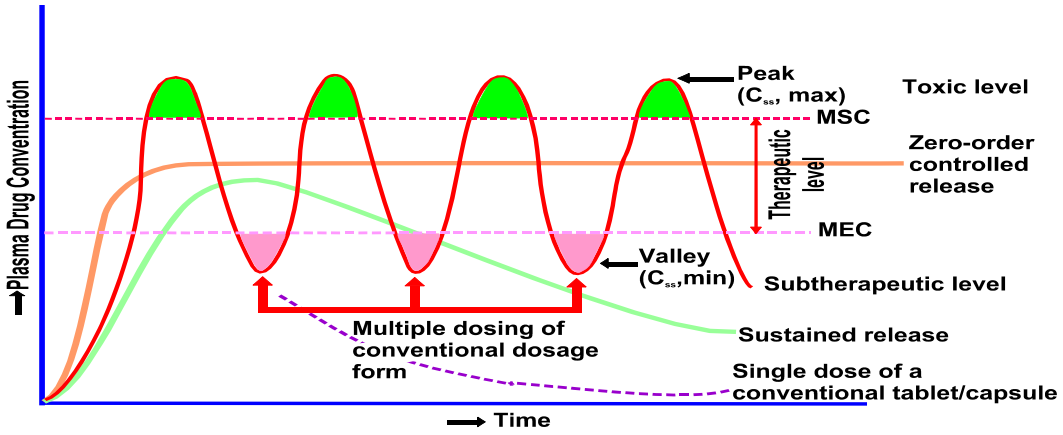

Fig. A hypothetical plasma concentration-time profile from conventional multiple dosing and single doses of sustained and controlled delivery formulations. (MSC = maximum safe concentration, MEC = minimum effective concentration).

Types of oral controlled release drug delivery systems[4]

A number of techniques are used to achieve controlled release of drugs via the oral cavity. The majority of the oral controlled release systems relay on dissolution, diffusion or a combination of both mechanisms to generate slow release of drug.

- Dissolution controlled release systems
- Diffusion controlled release systems
- Diffusion and dissolution systems
- Osmotically controlled release systems
- Gastroretentive drug delivery systems
- Electrically stimulated release devices
- Ion-exchange resins

1.2: Introduction to use of natural polymer in novel drug delivery systems:[5]

Polymer is any component other than the active substance(s) intentionally added to formulation of a dosage form. The use of natural polymer to deliver the bioactive agents has

been hampered by the synthetic materials. However advantages offered by these natural excipients are their being non-toxic, less expensive and freely available. The performance of the polymer partly determines the quality of the medicines. Present day consumers look for natural ingredients in food, drugs, and cosmetics as they believe that anything natural will be safe and devoid of side effects. The traditional view that excipients are inert and do not exert any therapeutic or biological action or modify the biological action of the drug substance has changed and it is now recognized that excipients can potentially influence the rate and/or extent of absorption of a drug. As herbal excipients are non toxic and compatible, they have a major role to play in pharmaceutical formulation.

Polysaccharides:

Natural polysaccharides are extensively used for the development of solid dosage forms. These polymers of monosaccharide's (sugars) are inexpensive and available in a variety of structures with a variety of properties. They are highly stable, safe, non-toxic, and hydrophilic and gel forming in nature. Pectins, starch, guar gum, amylase and karaya gum are a few polysaccharides commonly used in dosage forms.[6]

Pectins:

Pectins are non-starch, linear polysaccharides extracted from the plant cell walls. Pectin has been investigated as an excipient in many different types of dosage forms such as film coating of colon-specific drug delivery systems when mixed with ethyl cellulose, microparticulate delivery systems for ophthalmic preparations and matrix type transdermal patches. The capacity as an extrusion aid was found to be high; even formulations containing only 20% pectinic acid resulted in nearly spherical pellets. All pectinic acid pellets were mechanically stable, had an aspect ratio of approximately 1.15-1.20 and released 30-60% of a low solubility model drug within 15 min both in simulated gastric fluid.

Alginates:

Alginates are natural polysaccharide polymers isolated from the brown sea weed (Phaeophyceae). Alginic acid can be converted into its salts, of which sodium alginate is the major form currently used. A linear polymer consisting of D-mannuronic acid and L-guluronic acid residues arranged in blocks in the polymer chain, these homogeneous blocks (composed of either acid residue alone) are separated by blocks made of random or alternating units of mannuronic and guluronic acids. Alginates offer various applications in drug delivery, such as in matrix type alginate gel beads for local applications and to deliver the bio molecules in tissue engineering applications.[7]

Starches:

It is the principal form of carbohydrate reserve in green plants and especially present in seeds and underground organs. Starch occurs in the form of granules (starch grains), the shape and size of which are characteristic of the species, as is also the ratio of the content of the principal constituents, amylose and amylopectin. These include maize (*Zea mays*), rice (*Oryza sativa)*, wheat (*Triticum aestivum*), and potato (S *olanum tuberosum*).[8]

Gums and mucilages:

Gums are translucent and amorphous substances produced by the plants. Usually pathological products, gums are produced when the plant is growing under unfavorable conditions or when injured. Gums are plant hydrocolloids and may be anionic or non ionic polysaccharides. On hydrolysis gums yield sugar and salts of uronic acid.

Mucilages is a term that was used to describe the slimy aqueous dispersions produced by plants, animals and microbes, which consist basically of water-soluble polysaccharides including starches and modified starches. Gums and mucilage are used in many pharmaceutical applications such as emulsifyers, suspending agents, binders and disintegrants as well as sustaining agents in tablets and as gelling agents.

The use of natural mucilage's has following advantage.

- Local accessibility
- Environment friendly
- Lower prices as compared to imported synthetic product
- Non toxic and non-irritant[9]

2 LITERATURE REVIEW

Nep E. *et al.*[10] Prepared matrix-based tablets using different concentrations of Grewia gum, and the model drug ibuprofen, using a wet granulation technique. There was evidence suggesting synergism between grewia gum and guar gum in sustaining the release of ibuprofen from tablets when used in the ratio 2:1. Grewia gum may therefore prove a useful excipient,

Suresh.S *et al.*[11] Fabricated Sustained release tablets of Isoniazid using guar gum and carbapol, Tragacanth Gum and PEG-6000, in different proportion and combinations by direct compression technique. Results of in vitro release profile indicated that formulation (F2) was the most promising formulation as the extent of drug release from this formulation was high as compared to other formulations.

Chitta S. K. *et al.*[12]Developed matrix tablets of Diclofenac sodium with *Hibiscus rosa-sinensis* leaves mucilage and to study its functionality as a matrix forming material for sustained release tablet formulations.

Rajesh K. S. *et al.*[13] Developed controlled delivery of highly water soluble propranolol hydrochloride (PPHCl) using hydrophilic natural gums xanthan gum [X] and locust bean gum [LBG].

Deshmukh V.N. *et al.*[14] Evaluated oral sustained drug delivery system for Metoprolol succinate using natural hydrophilic gums such as karaya gum and xanthan gum as a release modifier. Among the formulations studied, formulation containing combination of KG and XG (2:8) having concentration of 20% showed sustained release of drug for 12 h with cumulative percent release of 99.24%.

Jain S. et al.[15] Fabricated Sustained release tablets of furosemide using pectin, guar gum and xanthan gum. A better controlled drug release (80.74%) was with the matrix tablet (G4) made-up of the guar gum than with the pectin and xanthan gum.

Emami J. *et al.*[16] Prepared sustained-release matrix tablets of flutamide by direct compression method using cellulose ethers (HPMC and NaCMC), natural gums (guar and xanthan gums) and compressible Eudragits (RSPO and RLPO) and their combinations were used in different ratios to examine their influence on tablet properties and drug release profile.

Panda D. S *et al.*[17] Found out the potential of gum from *Moringa oleifera* to act as a binder and release retardant in tablet formulations. The effect of calcium sulphate dihydrate (water insoluble) and lactose (water soluble) diluents on the release of propranolol hydrochloride was studied.

Chowdary K. P. *et al.*[18] Evaluated Olibanum and its resin and carbohydrate fractions as rate controlling matrix materials in tablets for controlled release of diclofenac. Diclofenac matrix tablets formulated employing olibanum and its resin component provided slow and controlled release of diclofenac over more than 24 hr. Drug release from the matrix tablets was by Fickian diffusion and followed first order kinetics.

Fukuda M.*et al.*[19]Investigated the influence of pH, buffer species and ionic strength on the release mechanism of chlorpheniramine maleate (CPM) from matrix tablets containing chitosan and xanthan gum prepared by a hot-melt extrusion process.

Varshosaz J. *et al.*[20] Developed matrix sustained-release tablets of highly water-soluble tramadol HCl using natural gums (xanthan and guar gum) compared with the extensively investigated hydrophilic matrices [HPMC, CMC]

3. OBJECTIVE / PROPOSED HYPOTHESIS:

Reviewed literature survey shows that, in conventional oral drug delivery systems, there is very little control over release of drug. After complete absorption of the drug from the dosage form, plasma drug concentrations decline according to the drug's pharmacokinetic profile. Eventually, plasma drug concentrations fall below the minimum effective plasma concentration (MEC), resulting in loss of therapeutic activity. In order to overcome this drawback of conventional drug delivery systems, it is aimed to Design and develop a novel controlled release oral formulation containing natural polymers, that could revolutionize method of medication and provide a number of therapeutic benefits.

To achieve this aim various objectives were charted out which are as follows:

1. Identification, collection and authentication of regional plants containing natural polymers in ample amount.
2. Isolation of the polymer from plant material by suitable isolation technique.
3. To develop controlled release oral formulation by using isolated natural polymers.
4. Selection and optimization of polymer concentration, that has pronounced effect on properties and drug release profile of the formulations.
5. Evaluation of various Physical and mechanical parameters of formulation.
6. To compare dissolution profile of the formulated product with marketed controlled release product.

4. METHODOLOGY TO BE ADOPTED:-

4.1.

Isolation / separation of natural polymer by suitable method of isolation / separation viz. Infusion, Decoction, Maceration, Percolation, Digestion etc. and by using a suitable solvent.

4.2.

Physical and Phytochemical evaluation of isolated polymer by performing different tests.

4.3.

Procurement of API followed by pre formulation study.

4.4.

Development of controlled release oral formulation using isolated natural polymer as an excipient by using suitable technique viz. wet granulation / dry granulation/ direct compression etc.

4.5.

Evaluation of the

1. Physical and mechanical Parameters as per official text.
2. Swelling behavior of controlled release Formulation
3. *In-vitro* drug release study
4. Accelerated stability studies

4.6.

Compilation of data

The prepared batches were evaluated for physical, mechanical parametric test (drug assay, diameter, thickness, hardness and tensile strength) swelling behavior and in vitro drug release would be studied. Accelerated stability studies would be also conducted on all the prepared batches. . The release kinetic and mechanism of release will be calculated by fitting in vitro release data in various kinetic models.

5. SIGINIFICANCE OF STUDY

Herbal natural polymer is used by their lack of toxicity, easy availability, and economic considerations in pharmaceutical industry as compared to their synthetic counterparts. Present day consumers look for natural ingredients in food, drugs, and cosmetics as they believe that anything natural will be more safe and devoid of side effects.

The traditional view that natural polymers are inert and do not exert any therapeutic or biological action or modify the biological action of the drug substance has changed and it is now recognized that natural polymers can potentially influence the rate and/or extent of absorption of a drug. As natural polymers are non toxic and compatible, they have a major role to play in pharmaceutical formulation. Hence an attempt will be made to use herbal natural polymers in Novel controlled release formulation.

Matrix technologies have often proven popular among the oral controlled drug delivery technologies because of their simplicity, ease in manufacturing, high level of reproducibility, stability of the raw materials and dosage form and ease of scale-up.

The conventional doses release the entire drug in just few minutes and therefore the therapeutic concentrations are maintained for a short period of time generating a need for administration of another dose. Therefore an attempt will be made to formulate oral controlled release formulation of model drug which would release the drug over a extended time period ssof time is beneficial.

6. PLAN OF WORK:

- **Part One: (Problem selection and review of literature)**
    - Review of literature
    - Problem selection: Selection of plants and model drug
- **Part Two: (Problem feasibility)**
    - Procurement of plants materials and model drug.
    - Authentification of plants materials
- **Part Three: (Experimental work)**
    - Extraction and Isolation of Polymers from Plant Materials
    - Preformulation studies of natural Polymers and model drug
    - Drug and Polymer Interaction Study
    - Optimization of natural Polymer concentration for formulation
    - Preparation of controlled release Formulation
    - Evaluation of various batches for

    1. Evaluation of Physical, mechanical and other parameters as per official text.
    2. Swelling behavior of controlled release Formulation
    3. *In-vitro* drug release
    5. Accelerated stability studies
- **Part Four: Compilation of data**

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